Targeting MicroRNAs to Limit Myocardial Lipid Accumulation
Gary D. Lopaschuk, John R. Ussher

Obesity and type 2 diabetes mellitus are major health concerns, with the incidence rapidly rising in the world. Among their many complications is an increased risk of developing heart failure. This increased incidence of heart failure in obese and diabetic individual occurs even when corrected for the increased prevalence of hypertension and coronary artery disease that are associated with obesity. One of the potential mechanisms proposed to contribute to this development of heart failure in obesity and diabetes mellitus relates to alterations in cardiac energy metabolism. In particular, an excess supply and reliance of the heart on fatty acids can contribute to the development of lipotoxicity because of the accumulation of lipid intermediates, such as ceramide, that have direct toxic actions on cardiac myocytes. Furthermore, the accumulation of byproducts of incomplete fatty acid oxidation and the inhibition of glucose use by fatty acids are also thought to contribute to the development of obesity-related and diabetes mellitus–related heart failure. A key kinase involved in regulating cardiac energy metabolism is AMP-activated protein kinase (AMPK), which is involved in the control of fatty acid oxidation, as well as both glucose uptake and glycolysis. In obesity and diabetes mellitus, AMPK phosphorylation (which induces activation) in the heart is reduced, which may contribute to the lipotoxic changes. However, the mechanism(s) by which myocardial AMPK phosphorylation is decreased in obesity and diabetes mellitus is not fully understood. In this issue of Circulation Research, Kuwabara et al provide evidence that microRNAs regulate the lipotoxic process by controlling AMPK activity and myocardial ceramide content (Figure).

Because of their ability to repress gene transcription, numerous investigators have explored whether targeting microRNAs can be used to treat various cardiovascular diseases. Indeed, activating miRNA-214 has been shown to reduce ischemia/reperfusion injury via improving calcium handling, whereas activation of miRNA-204 reduces overall pulmonary arterial hypertension disease severity via enhancing pulmonary artery smooth muscle cell apoptosis. In contrast, reducing miRNA-155 activity ameliorates left ventricular (LV) remodeling and heart failure via decreasing cardiac myocyte hypertrophy.

Adding to the rapidly growing body of evidence suggesting that miRNA manipulation is an exciting new approach to treat various cardiovascular diseases, Kuwabara et al have now shown that miRNAs also contribute to obesity/diabetes mellitus–associated cardiomyopathy. Kuwabara et al demonstrated that 20 weeks of high-fat feeding (45% kcal from lard) increases miRNA-451 expression in the heart, whereas exposure to increasing concentrations of the fatty acid palmitate, which is elevated in patients with obesity, also increases miRNA-451 expression in neonatal rat cardiac myocytes. In addition, lentiviral-mediated overexpression of miRNA-451 in neonatal rat cardiac myocytes increases cellular apoptosis, whereas this effect is partially blunted in neonatal rat cardiac myocytes treated with an miRNA-451 decoy antagonist. Interestingly, Kuwabara et al demonstrated that the cardiotoxic effect of increased miRNA-451 expression was partly due to the miRNA-451 downstream target gene, calcium-binding protein 39, since calcium-binding protein 39 overexpression partially reversed the deleterious effects of high palmitate on neonatal rat cardiac myocyte survival.

To complement their in vitro studies, Kuwabara et al generated cardiac-specific miRNA-451-deficient (miRNA-451Heart−/−) mice, and showed that these mice were protected against obesity (20 weeks of high-fat feeding, 60% kcal from lard)–induced cardiomyopathy. This included a reduction in cardiac hypertrophy and an improved functional reserve during cardiac catheterization studies in response to dobutamine stress. Moreover, the cardioprotection against obesity-induced cardiomyopathy in miRNA-451Heart−/− mice was attributed to increased AMPK activity. Because increased AMPK activity increases fatty acid oxidation rates, the authors hypothesized that myocardial lipid intermediates, which are increased in the heart during obesity and type 2 diabetes mellitus, would be reduced (Figure). Supporting their hypothesis, myocardial ceramide content measured via immunohistochemistry was indeed lower in miRNA-451Heart−/− mice versus their control littermates. Therefore, Kuwabara et al concluded that miRNA-451 precipitates cardiac lipotoxicity during high-fat diet–induced obesity through suppression of AMPK activity.

These findings add to the multitude of evidence highlighting AMPK activation as an exciting target to improve cardiac function in the setting of obesity and diabetes mellitus. For example, the first-line therapy for the treatment of type 2 diabetes...
Figure. Proposed mechanism of miRNA-451-mediated cardioprotection against obesity-related cardiomyopathy. Kuwabara et al11 postulate antagonizing miRNA-451 activity in the myocardium protects against obesity-induced cardiomyopathy via activation of AMP-activated protein kinase (AMPK), which through an undefined mechanism leads to a reduction in cardiac myocyte ceramide content, reducing cellular hypertrophy and improving contractile functional reserve.

mellitus, metformin, has been suggested to mediate its beneficial effects through activation of AMPK, and a single low-dose treatment of metformin (125 μg/kg) at either the induction of ischemia or during the onset of reperfusion has been shown to enhance LV function and reduce infarct size in an AMPK-dependent manner in diabetic db/db mice.20 Induction of autophagy may also contribute to the protective effects of AMPK against diabetic cardiomyopathy because treatment of diabetic OVE26 mice with metformin (200 mg/kg per day) increased autophagy and LV function, whereas these effects were absent in metformin-treated diabetic-dominant negative AMPKα2 transgenic mice.21 Furthermore, treatment with metformin (100 mg/kg per day) for 1 year increased AMPK phosphorylation (indicative of AMPK activity), reduced myocardial lipid content, and improved LV function in obese and insulin-resistant spontaneously hypertensive and heart failure–prone rats.22

Although the aforementioned studies suggest that AMPK may indeed be a novel cardioprotective target, AMPK activation in the heart is not necessarily associated with improved LV function under all circumstances, such as during ischemia/reperfusion injury where AMPK activation of fatty acid oxidation reduces the recovery of contractile efficiency.7,23 Moreover, AMPK has a broad range of diverse actions,3 some beneficial and others harmful, and as such it is difficult to attribute the observed cardioprotection in the study of Kuwabara et al11 strictly to AMPK activation. Because fatty acid oxidation rates are already markedly elevated in the obese or diabetic heart,3,24 an additional increase in fatty acid oxidation via AMPK activation is unlikely to account for reduced myocardial lipid accumulation. Indeed, total myocardial neutral lipid (ie, triacylglycerol) content was similar between miRNA-451Heart−/− mice and their control littermates, thus AMPK-independent actions involved in ceramide metabolism may account for the reduction in myocardial ceramide content in miRNA-451Heart−/− mice. A reduction in ceramide content yields favorable effects on the myocardium, including improvements in myocardial glucose metabolism during high-fat diet–induced obesity, whereas attenuating lipotoxic cardiomyopathy in mice with a cardiac-specific overexpression of glycosylphosphatidylinositol-anchored human lipoprotein lipase.18,25 However, it is somewhat surprising that the authors observed an increase in myocardial ceramide content with high-fat feeding, as other studies have not reported an appreciable increase in myocardial ceramide levels in response to obesity.8,19,26 which has been recapitulated in myocardial samples from patients with obesity/type 2 diabetes mellitus.27 Conversely, myocardial ceramide content is increased in middle-aged (40–44 weeks old) mice fed a high-fat diet for 3 months.26 Nonetheless, the technique used to quantify ceramide content in this particular study that has not been validated against more standard measures, such as high-performance liquid chromatography and gas chromatography/mass spectrometry. Hence, it remains to be determined whether alterations in ceramide content are truly responsible for miRNA-451’s contribution to lipotoxic cardiomyopathy.

Taken together, the observations of Kuwabara et al11 are of high clinical relevance because of the large obese patient population at risk for cardiovascular disease. Thus, there is a need to develop novel treatments for obesity-associated or diabetes mellitus–associated cardiomyopathy, which to date do not have any specific-tailored therapies approved for clinical use. A miRNA-451 antagonist seems to be a suitable and exciting candidate that may change this situation, although at this stage all miRNA-based therapies in development for any human disease are currently in preclinical stages or phase 1 trials to assess overall safety profiles. Future studies should use pharmacological approaches to determine whether miRNA-451 inhibition mimics the effects observed in miRNA-451Heart−/− mice. Moreover, it will be essential to determine whether miRNA-451 inhibition also confers protection against ischemic heart disease and heart failure in the setting of obesity because patients with obesity are at increased risk for both these disorders, where alterations in fatty acid metabolism significantly contribute to the underlying pathology.

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Disclosures

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